DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Via Federal Express

AUG 21 2003

WARNING LETTER

Robert A. Bishop, II
President
Silimed, Incorporated
11220 Grader Street, Suite 100
Dallas, Texas 75238

Dear Mr. Bishop:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection at your facility and to request a written response.

On January 13-29, 2003, Ms. Cynthia A. Harris and Mr. Phillip D. Waldron, investigators from FDA's Dallas District Office, conducted an inspection at Silimed, Inc. The purpose of the inspection was to determine whether your activities as a sponsor of investigational studies with significant risk devices, intended for use for [redacted] and [redacted] complied with applicable FDA regulations.

FDA investigators conducted this inspection under a program designed, in part, to ensure that data and information contained in applications for an Investigational Device Exemption (IDE) are scientifically valid and accurate. Another objective of this program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

At the close of the inspection, the FDA investigators issued a Form FDA-483, "Inspectional Observations," and discussed the findings with you. The deviations listed below are not intended to be an all–inclusive list of violations observed at your facility. As a sponsor of investigational studies, it is your responsibility to ensure that devices you ship and investigations you sponsor comply with applicable FDA regulations. The following violations were observed:

1. **You distributed significant risk devices without an FDA approved IDE or premarket approval application (PMA). Consequently, these devices are adulterated under section 501(f)(1)(A) of the Act (21 U.S.C. § 351(f)(1)(A)).**

Silimed's records disclose that between October 2000 and January 2003, Silimed sold at least 80 unapproved significant risk devices --[redacted]-- to at least 15 different hospitals or physicians

throughout the United States. The unapproved devices were implanted without the knowledge or approval of the FDA, without proper Institutional Review Board (IRB) oversight, and, in most cases, without the patient knowing that the devices were unapproved and investigational.

2. **Failure to obtain IRB review and approval of Silimed [redacted] and [redacted] under IDE [redacted] (21 CFR 56.103 and 21 CFR 812.42).**

Silimed's records indicate that the company distributed more than 500 devices to at least 25 different medical establishments that did not receive IRB approval before initiating their site investigations. Nine of the medical establishments never received IRB review and approval of the clinical investigation at their site.

3. **Failure to ensure proper monitoring of the clinical investigation and to secure prompt investigators' compliance with the investigational plan and applicable FDA regulations (21 CFR 812.40 and 812.46).**

As the sponsor, you are responsible for monitoring the investigators' activities [21 CFR 812.40]. You are also responsible for securing their compliance with the investigational plan, the requirements of applicable FDA regulations, and any conditions of approval imposed by FDA or the reviewing IRB [21 CFR 812.46].

Our inspection of the clinical investigation under IDE [redacted] revealed a number of violations associated your commitments in the IDE. The IDE monitoring plan states that the clinical monitor will cover FDA regulations, protocol, IRB approval, case report forms, record keeping requirements, administrative reports, and the adequacy of facilities during a pre-investigational (study initiation) site visit. Your monitoring procedures state that the monitor will ensure that a valid investigator's agreement, confidentiality agreement, financial disclosure, and IRB approval are in place before signing off for the initial shipment of the device to a new (clinical) investigator. There is no documentation of a study initiation visit to [redacted], and [redacted] There is no documentation of sign off by the clinical monitor before the devices were shipped to the clinical sites.

Furthermore, the IDE monitoring plan requires the Clinical Monitor to conduct monitoring visits at each investigational site. No other sponsor's representative is identified as a site monitor. The only records documenting visits by the Clinical Monitor were for seven of 60 clinical investigators' locations. Other records documented site visits by contract sales representatives.

Written monitoring procedures state that monitoring activities are to be documented in a designated format including use of the Site Visit Monitoring Report and Monitoring Visit

Observation Report. With the exception of a site visit to the location of [redacted] by the Clinical Monitor, the site visits to the other three investigators whose records were reviewed by FDA were conducted by contract sales representatives and not documented.

Records collected during the inspection indicate you were aware as early as April 2002 that [redacted] and as early as March 2001 that [redacted] were noncompliant in their clinical investigations. [redacted] failed to provide information regarding follow-up visits of his 22 subjects enrolled between March 2001 and August 2001. [redacted] failed to complete case histories of 66 subjects enrolled between November 21, 2000, and August 6, 2000. However, you made no effort to secure compliance promptly with these clinical investigators. You did not terminate [redacted] and [redacted] until July 23, 2002. A sponsor who discovers that an investigator is not complying with the investigational plan, the requirements of 21 CFR Part 812, or other applicable FDA regulations shall promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation [21 CFR 812.46].

4. Failure to maintain complete and current records relating to the clinical investigation [21 CFR 812.140(b)(1) and 812.140(b)(3)]

Silimed failed to maintain correspondence with the monitors, investigators, IRBs, and FDA [21 CFR 812.140(b)(1)]. The firm did not have complete correspondence between the sponsor and clinical investigators and between the monitors and clinical investigators. Also, the firm did not have complete records of all progress reports submitted to the reviewing IRBs and complete records of reports to the FDA about clinical investigators using the device without obtaining informed consent. Silimed also did not maintain complete financial disclosure information for each clinical investigator [21 CFR 812.140(b)(3)].

5. Failure to prepare and submit complete, accurate, and timely reports related to the clinical investigation [21 CFR 812.150(b)(5) and 812.150(b)(8)]

Silimed failed to prepare and submit to FDA reports of investigators using the investigational device without obtaining consent from subjects. Your records contain instances where subjects were implanted with the investigational device without signing an IRB-approved consent form. For example, [redacted] implanted the Silimed [redacted] into seven subjects between June and July 2000, but the site did not receive IRB approval for the study until October 18, 2000. These incidents were not reported within the five working days to the FDA upon discovery by the sponsor [21 CFR 812.150(b)(8)]. Silimed also failed to submit annual progress reports to FDA and the reviewing IRB documenting these consent infractions and failure of the site to obtain IRB approval [21 CFR 812.150(b)(5)].

FDA considers your activities to be serious violations of the law. The introduction of adulterated devices is a violation of Section 301(a) of the Act (21 U.S.C. § 331(a)). Further use of the unapproved devices are violations of Section 301(q)(1) of the Act (21 U.S.C. § 331(q)(1)). Continuation of these activities may result in FDA taking regulatory action without further notice. These actions include, but are not limited to, seizure, injunction, civil money penalties, or criminal prosecution.

Please respond to this letter in writing within 15 days. Your response should include distribution information for the [redacted] and any other unapproved devices. This information should include the name, address, and phone number of practitioners and institutions receiving the devices and the dates of shipment.

To protect the rights and welfare of the human subjects you implanted, you must develop a corrective action plan that includes at a minimum, notification of each recipient by certified mail that they were implanted with an unapproved device, who to contact in the event of an emergency, and where to report adverse events. Your corrective action plan should be submitted to this office for approval before implementation. Copies of all letters sent to implant recipients should also be submitted to this office.

In addition, please submit a written corrective action plan that includes documentation of the specific steps you have taken or will take to correct and prevent the recurrence of similar violations in current and future clinical investigations. Your response must include timeframes for completion of corrective actions and copies of any agreements with, and the qualifications of, any third-party auditors or contractors you may choose to use.

We acknowledge receipt of your response to the FDA-483 dated March 13, 2003. We disagree with your assertion that the [redacted] is a custom device and that you were acting as a contract manufacturer for [redacted]. The custom device exemption of section 520(b) of the Act (21 U.S.C. § 360j(b)) extends a limited exemption to the mandatory performance standard requirements of section 514 of the Act (21 U.S.C. § 360d) and the PMA requirements of section 515 of the Act (21 U.S.C. § 360e) to devices that meet a narrow and specific set of statutory requirements. In addition, by regulation FDA has extended the concept of a custom device exemption to IDEs through provisions found at 21 CFR 812.2(c)(7) and 812.3(b). Among those requirements, a custom device must be intended for use by an individual patient named in a prescription and made in a special form for that patient or must be intended to meet the special needs of a particular health professional in the course of his professional practice. A special need is one that relates to unusual anatomical features of the individual physician for whom the device was produced, or to special needs of his or her practice that are not shared by other health professionals of the same specialty. A device that meets a need that is shared by others in the field is a device that can be tested through clinical investigations and can be subject to the PMA requirements in order to ensure that it is safe and effective. These requirements

are to be narrowly construed and do not create an exemption from otherwise applicable statutory requirements.

Custom device exemptions are not mandated by statute. Neither the IDE nor premarket notification regulations exempt from its respective requirements a broader category of devices than 520(b) of the Act exempts from the requirements of a PMA. Consequently, a device that could not qualify for a custom device exemption under section 520(b) also can not qualify for an exemption from IDE requirements under 21 C.F.R. 812.2(c)(7).

The [redacted] devices distributed by Silimed to different hospitals, physicians, and/or medical device distributors do not meet the criteria for a custom device explained above and, therefore, are not exempt from compliance with the premarket notification requirements, the investigational device exemption regulations, or premarket approval requirements. Your other responses lack appropriate detail and, in some cases, indicate a fundamental lack of understanding regarding a sponsor's responsibilities when conducting a clinical trial.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ-311), 2098 Gaither Road, Rockville, Maryland 20850. Attention: Kevin M. Hopson, Consumer Safety Officer. Please direct all questions concerning this matter to Mr. Hopson at (301) 594-4720, ext. 128.

A copy of this Warning Letter was sent to the Food and Drug Administration's Dallas District Office, 4040 North Central Expressway, Suite 300, Dallas, Texas 75204. We request that a copy of your response also be sent to that office.

Sincerely yours,

Michael E Marcarelli

for Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc: PURGED COPIES

[redacted]
Chairman
Western Institutional Review Board, Incorporated
3535 Seventh Avenue, S.W.
Olympia, Washington 98502-5010